



Complete Summary

GUIDELINE TITLE

Practice parameters for the treatment of narcolepsy: an update for 2000.

BIBLIOGRAPHIC SOURCE(S)

Littner M, Johnson SF, McCall WV, Anderson WM, Davila D, Hartse SK, Kushida CA, Wise MS, Hirshkowitz M, Woodson BT. Practice parameters for the treatment of narcolepsy: an update for 2000. Sleep 2001 Jun 15;24(4):451-66. [58 references]

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SCOPE

DISEASE/CONDITION(S)

Narcolepsy

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pediatrics
Psychiatry
Sleep Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To update the 1994 practice parameters for treatment of narcolepsy

TARGET POPULATION

Adults and children diagnosed with narcolepsy

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Establishment of individual treatment objectives
2. Medications:
 - Modafinil
 - Amphetamine, methamphetamine, dextroamphetamine, methylphenidate
 - Selegiline
 - Pemoline
 - Tricyclic antidepressants
 - Fluoxetine
 - Combinations of long- and short-acting forms of stimulants
3. Scheduled naps
4. Regular follow-up:
 - Monitoring of response to treatment (e.g., by interview, self-report questionnaires [the Epworth Sleepiness Scale], maintenance of wakefulness test [MWT] or the multiple sleep latency test [MSLT])
 - Assessing for and responding to potential side effects of medications
 - Measures to enhance patient's adaptation to the disorder such as patient education of disease management, assistance with occupational and social accommodation for disabilities

MAJOR OUTCOMES CONSIDERED

- Efficacy of treatment for narcolepsy in reducing daytime sleepiness, improving daytime alertness, and improving normal functioning as determined by multiple subjective and objective measures
- Quality of life
- Adverse effects of and tolerance to medications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Medline was searched from 1993 through and including articles published up to August 2000 with subject headings narcolepsy or cataplexy. In addition, human clinical trials, Americans with Disabilities Act, quality of life, driving, and compliance each were used as limiting terms. Finally, pemoline and methylphenidate were used as subject headings to discover information about toxic side effects. For information about teratogenicity, a textbook about prescription medication use in pregnancy was employed. Case reports, abstracts, editorials, letters, and reviews were excluded except for reports of adverse effects of treatments. Examination of the reference lists from the articles found in the Medline search provided a few relevant studies from literature published prior to 1993. For an economic indicator about drug costs, the wholesale price, as listed in the Drug Topics Red Book Update was used.

NUMBER OF SOURCE DOCUMENTS

The Medline search for narcolepsy and clinical trials yielded 29 articles, of which 14 were relevant to this paper. The Medline search of narcolepsy and human returned 450 articles. In the narcolepsy and human search, several clinical trials were found which did not show up in the more limited search. The Medline search for narcolepsy and compliance yielded one relevant article. The search for narcolepsy and driving yielded 26 references, of which six proved relevant. Narcolepsy and quality of life yielded 15 references of which three proved to contain original data. Other articles about quality of life in narcolepsy were found in the reference sections of these articles. Although the search under Americans with Disabilities Act yielded 469 references, none were directly related to narcolepsy. The search under cataplexy yielded 169 articles, of which 36 were human clinical studies, but many turned out to be case reports or small case series.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Recommendation Grades

A (Evidence Level I)

- Randomized well-designed trials with low-alpha & low-beta errors*

B (Evidence Level II)

- Randomized trials with high-beta errors*

C (Evidence Level III)

- Nonrandomized controlled or concurrent cohort studies

C (Evidence Level IV)

- Nonrandomized historical cohort studies

C (Evidence Level V)

- Case series

* Alpha error refers to the probability (generally set at 95% or greater) that a significant result (e.g., $p < 0.05$) is the correct conclusion of the study or studies. Beta error refers to the probability (generally set at 80% or 90% or greater) that a nonsignificant result (e.g., $p > 0.05$) is the correct conclusion of the study or studies. The estimation of beta error is generally the result of a power analysis. The power analysis includes a sample size analysis which projects the size of the study population necessary to ensure that significant differences will be observed if actually present.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

All clinical trials of therapy were considered for the evidence tables. Case series and database articles about diagnosis of narcolepsy were incorporated in the evidence tables only if they included greater than 20 subjects.

The American Academy of Sleep Medicine rated the recommendations of this paper as standards, guidelines, and options, based on evidence from studies published in peer-reviewed journals that were evaluated as noted in the evidence tables.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When scientific data were insufficient or inconclusive, recommendations were based on consensus opinion.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Levels of Recommendation

Standard

- This is a generally accepted patient-care strategy which reflects a high degree of clinical certainty. The term standard generally implies the use of Level I

Evidence, which directly addresses the clinical issue, or overwhelming Level II Evidence.

Guideline

- This is a patient-care strategy which reflects a moderate degree of clinical certainty. The term guideline implies the use of Level II Evidence or a consensus of Level III Evidence.

Option

- This is a patient-care strategy which reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The Board of Directors of the American Academy of Sleep Medicine reviewed the Standards of Practice Committee (SPC) for material conflicts of interest relevant to the recommendations and approved the final version of the parameters prior to publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations are given as standards, guidelines, and options as defined below. The recommendation grades (A-C) and levels of evidence (I-V) are defined at the end of the Major Recommendation field.

Levels of Recommendation

Standard

- This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of Level I Evidence, which directly addresses the clinical issue, or overwhelming Level II Evidence.

Guideline

- This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of Level II Evidence or a consensus of Level III Evidence.

Option

- This is a patient-care strategy that reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.
1. An accurate diagnosis of narcolepsy should be established which shall include a thorough evaluation of other possible contributing causes, apart from narcolepsy, to the excessive daytime sleepiness (Standard).

For patients suspected of having narcolepsy, an all-night polysomnogram is done primarily to ascertain the presence of concurrent sleep disorders and is followed immediately by a multiple sleep latency test (MSLT) to help confirm the diagnosis. The multiple sleep latency test also helps determine the severity of daytime sleepiness. The reader is referred for diagnostic criteria (refer to Table 4 in the original guideline document). Other methods to evaluate sleepiness include objective tests such as the maintenance of wakefulness test (MWT), and subjective approaches such as the Epworth Sleepiness Scale. This part of the recommendation is based on committee consensus and is similar to a recommendation made previously.

Chronic daytime sleepiness is a nonspecific symptom and conditions that produce such sleepiness may coexist with narcolepsy. For example, the obstructive sleep apnea syndrome (OSAS) and periodic limb movement disorder (PLMD) may be present as determined by the results of the all-night polysomnogram. Insufficient sleep, idiopathic hypersomnia, inadequate sleep hygiene, and circadian rhythm disorders, among others should be considered as possible contributors to sleepiness independent of narcolepsy. Management of other disorders possibly contributing to sleepiness in a patient with narcolepsy may require approaches apart from stimulants to treat sleepiness either directly or as therapy of the underlying condition. This part of the recommendation is new and is based on committee consensus.

2. Individual treatment objectives should be established for each patient with narcolepsy to improve quality of life (Standard).

One level II, grade B, four level III, grade C, and one level V, grade C, studies, and committee consensus, provide evidence that symptoms of narcolepsy may adversely impact quality of life (Refer to Tables 3 and 4 in the original guideline document). In keeping with the previous practice parameters, a major objective of treatment should be to alleviate daytime sleepiness with stimulants. The goal should be to produce the fullest possible return of normal function for patients at work, at school, at home, and socially. A new recommendation is to control cataplexy, hypnagogic hallucinations, and sleep paralysis, when present and troublesome. The health care provider should consider the benefit-to-risk ratio of medication for an individual patient, the cost of medication, convenience of administration, and

the cost of ongoing care including possible laboratory tests when selecting a medication for treatment of narcolepsy.

3. The following medications are effective treatments for narcolepsy. Comparative safety and efficacy of the stimulant medications are not defined. The rating of the recommendation is based on the grade of evidence for each. Refer to Table 5 in the original guideline document for dosages.
 - a. Modafinil is effective for treatment of daytime sleepiness due to narcolepsy (Standard). [Refer to Table 3 of the original guideline document] This conclusion is based on the favorable benefit-to-risk ratio for modafinil established in three level I, grade A studies with confirmation from additional studies. This is a new recommendation.
 - b. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy (Guideline). [Refer to Table 3 of the original guideline document] These medications are mainstays of narcolepsy treatment. Based on 3 level II, grade B and 4 level V, grade C studies and long clinical practice, they have a long record of efficacy. However, the benefit-to-risk ratio is not well documented, because the published clinical trials include only small numbers of patients. This recommendation is similar to that made previously.
 - c. Selegiline is an effective treatment for all narcoleptic symptoms (Guideline). [Refer to Table 3 of the original guideline document] Based on two level II, grade B and one level IV, grade C studies, selegiline is effective, but the cost of the medication is very high, experience with the high doses needed for narcolepsy is limited, and diet-induced hypertension is a danger at effective doses. This is a new recommendation.
 - d. Pemoline is effective for treatment of daytime sleepiness in narcolepsy (Option). [Refer to Table 3 of the original guideline document] Pemoline can produce rare and potentially lethal liver toxicity that may be unpredictable. Because of this toxicity, the use of pemoline in patients with narcolepsy is rarely indicated. Based on one level II, grade B study, pemoline may be less potent than amphetamines, but adherence to pemoline therapy may be better than adherence to amphetamines or methylphenidate. This is a modification of a recommendation made previously. In particular, the warning on liver toxicity is emphasized to a greater degree than previously.
 - e. Tricyclic antidepressants and fluoxetine may be effective treatment for cataplexy, sleep paralysis, and hypnagogic hallucinations (Guideline). [Refer to Table 4 of the original guideline document] The recommendation for tricyclic agents is based on one level V, Grade C study, long clinical experience and committee consensus. This is a new recommendation. The recommendation for fluoxetine is based on one level II, grade B and one level V, grade C study. This is a new recommendation.
 - f. Combinations of long- and short-acting forms of stimulants may be effective for some patients (Option). Some stimulants have a short (3 to 4 hour) effective period (e.g., methylphenidate). Others have longer duration of activity and longer onset of action (e.g., modafinil, sustained release amphetamine). By combining stimulants with different activity characteristics, it may be possible to

achieve alertness quickly and for longer periods of time and also not produce insomnia as an unwanted side effect. In addition, combinations of stimulants and antidepressants may be of benefit for treatment of sleepiness and REM-related symptoms such as cataplexy. For example, modafinil appears compatible with antidepressant medications, but published evidence is limited. This recommendation is similar to that made previously and is based on committee consensus.

4. Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy (Guideline). [Refer to Table 2 of the original guideline document] This recommendation is based on two level II, grade B, one level IV, grade C and one level V, grade C studies and long clinical experience. This recommendation is similar to that made previously.
5. Regular follow-up of patients with narcolepsy is necessary to monitor response to treatment, to respond to potential side effects of medications, and to enhance the patient's adaptation to the disorder (Standard).
 - a. A patient stabilized on stimulant medication should be seen regularly by a health care provider at least once per year, and preferably once every 6 months, to assess the development of medication side effects, including sleep disturbances, mood changes, and cardiovascular or metabolic abnormalities. This is the same recommendation as made previously and is based on committee consensus.
 - b. Follow-up is necessary to determine adherence and response to treatment; to monitor for the safety of medications in individual patients; and to assist the patient with occupational and social problems. Adherence to stimulant drug treatment in narcolepsy is impeded by inconvenient dosage, but not by age, educational level, gender, or response to therapy. Of note, many patients with narcolepsy cannot be restored to normal levels of daytime alertness, even when adhering to optimum doses of stimulant medications (Refer to Table 5 of the original guideline document). Most often, response to therapy can be determined by interview of the patient and associates as well as by self-report questionnaires, such as the Epworth Sleepiness Scale. Objective measures, such as the maintenance of wakefulness test (MWT) or the multiple sleep latency test (MSLT), may play a role when occupational or public safety concerns are at issue. This is an expansion of a similar recommendation made previously and is based on committee consensus.
 - c. Patients with severe sleepiness should be advised to avoid potentially dangerous activities at home and at work, and should not operate a motor vehicle until sleepiness is appropriately controlled by stimulant medications. This recommendation is the same as that previously and is based on one level II, grade B and one level III, grade B study (Refer to Table 4 of the original guideline document) and committee consensus.
 - d. Of the stimulants used to treat narcolepsy, amphetamines, especially at high doses, are the most likely to result in the development of tolerance. This is the same recommendation as previously. Reiteration of the discussion and literature cited in the previous review paper are beyond the scope of the current review and the reader is referred for further information.

- e. Patients who fail to respond to adequate doses of stimulant medication should be carefully assessed for other sleep disorders such as insufficient sleep, inadequate sleep, hygiene, circadian rhythm disorders, obstructive sleep apnea syndrome, or periodic limb movement disorder, that may contribute to excessive sleepiness. This is essentially the same recommendation as previously and is based on committee consensus.
- f. For side effects, dosage ranges, use in pregnancy and by nursing mothers, class of medication and use in narcolepsy, see Table 5 in the original guideline document. The information found in Table 5 on stimulants is similar and, in some cases, an expansion of information provided previously. The information on the other classes of medications is new. Note that any of the stimulant medications can be abused.
- g. Treatment of narcolepsy with methylphenidate in children between the ages of 6 and 15 appears relatively safe, but caution must be used if other medications are employed. See Table 5 in the original guideline document for dosages. This recommendation is similar to that previously and is based on the considerable experience with use of methylphenidate for treatment of attention deficit disorder.
- h. Health care providers should assist the patient with occupational and social accommodation for disabilities due to narcolepsy. The Americans with Disabilities Act provides legal guidance. Patients deserve appropriate help from health care providers to insure that the intent of the law is realized. Because sustained alertness often is difficult to achieve even with optimum treatment, some patients should be advised to avoid potentially dangerous activities, such as driving, climbing, or working in the vicinity of dangerous machinery, which could result in injury to the patient or others. This recommendation is similar to that previously and is based on committee consensus.
- i. Polysomnographic reevaluation of patients should be considered if symptoms of sleepiness increase significantly or if specific symptoms develop that suggest new or increased sleep abnormalities as might occur in disorders such as sleep apnea or periodic limb movement disorder. This is the same recommendation as that previously and is based on committee consensus.

Definitions:

Recommendation Grades

A (Evidence Level I)

- Randomized well-designed trials with low-alpha & low-beta errors*

B (Evidence Level II)

- Randomized trials with high-beta errors*

C (Evidence Level III)

- Nonrandomized controlled or concurrent cohort studies

C (Evidence Level IV)

- Nonrandomized historical cohort studies

C (Evidence Level V)

- Case series

* Alpha error refers to the probability (generally set at 95% or greater) that a significant result (e.g., $p < 0.05$) is the correct conclusion of the study or studies. Beta error refers to the probability (generally set at 80% or 90% or greater) that a nonsignificant result (e.g., $p > 0.05$) is the correct conclusion of the study or studies. The estimation of beta error is generally the result of a power analysis. The power analysis includes a sample size analysis which projects the size of the study population necessary to ensure that significant differences will be observed if actually present.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

In general, these guidelines may have a positive impact on professional behavior, patient outcomes, and, possibly, health care costs.

The appropriate treatment of patients with narcolepsy may reduce daytime sleepiness, improve daytime alertness, allow return to normal functioning, improve quality of life, and minimize adverse effects of medication.

POTENTIAL HARMS

The following are major side effects (not in order of occurrence) and pregnancy risk categories* of recommended medications:

- Amphetamine, sustained release amphetamine, and methamphetamine: Insomnia, restlessness, tachycardia, psychotic episodes (rare), dizziness, diarrhea, constipation, hypertension, impotence. (Pregnancy risk category C**)
- Methylphenidate. Nervousness, insomnia, anorexia, nausea, dizziness, hypertension, hypotension, hypersensitivity reactions, tachycardia, headache, very rare reports of neuroleptic malignant syndrome. (Pregnancy risk category not established)
- Modafinil. Headache, nausea, eosinophilia, diarrhea, dry mouth, anorexia, (Pregnancy risk category not established)
- Pemoline: Seizures, liver failure, isolated case of aplastic anemia, insomnia, hallucinations, anorexia and weight loss. (Pregnancy risk category B)
- Selegiline: Nausea, dizziness, confusion, tremor, orthostatic hypotension, diet-induced hypertension. (Pregnancy risk category C)
- Fluoxetine. Asthenia, nausea, diarrhea, anorexia, insomnia, tremor, anxiety, somnolence. (Pregnancy risk category C)
- Protriptyline. Orthostatic hypotension, hypertension, seizures, headache, anticholinergic symptoms, impotence, impaired liver function, myocardial infarction, stroke. (Pregnancy risk category not established)

Any of the stimulant medications can be abused.

* The United States Food and Drug Administration (FDA) classifies drugs as A, B, C, D, or X, indicating increasing levels of toxicity, according to embryotoxic and teratogenic effects. Class A means controlled human studies show no risk to the human fetus in the first trimester and the possibility of fetal harm is remote, B means animal studies indicate no fetal risk, and there are no controlled human studies, C means animal studies have shown teratogenic or embryocidal effects, and there are no controlled human studies, D means there is evidence of risk to human fetuses but benefits may make risks acceptable, X means studies in animals or humans have demonstrated fetal abnormalities and the risks outweigh any possible benefit.

** Infants born to mothers on amphetamines may be premature, have low birth weight and experience withdrawal symptoms.

Subgroups Most Likely to be Harmed:

Pregnant women may be at additional risk of harm.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific care must be made by health care providers in light of the individual circumstances presented by the patient and the available diagnostic and treatment options as resources.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Littner M, Johnson SF, McCall WV, Anderson WM, Davila D, Hartse SK, Kushida CA, Wise MS, Hirshkowitz M, Woodson BT. Practice parameters for the treatment of narcolepsy: an update for 2000. Sleep 2001 Jun 15;24(4):451-66. [58 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1994 (updated 2001 Jun)

GUIDELINE DEVELOPER(S)

American Academy of Sleep Medicine - Professional Association

SOURCE(S) OF FUNDING

American Academy of Sleep Medicine (AASM)

GUIDELINE COMMITTEE

Standards of Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Members: Michael Littner MD; Stephen F. Johnson MD; W. Vaughn McCall MD, MS; W. McDowell Anderson MD; David Davila MD; Kristyna Hartse PhD; Clete A. Kushida MD, PhD; Merrill S. Wise MD; Max Hirshkowitz PhD; B. Tucker Woodson MD, FACS.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Board of Directors of the American Academy of Sleep Medicine reviewed the Standards of Practice Committee for material conflicts of interest relevant to the recommendations and approved the final version of the parameters prior to publication.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline is an update of a previously issued version (Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of stimulants in the treatment of narcolepsy. *Sleep* 1994;17[4]:348-51).

GUIDELINE AVAILABILITY

Electronic copies: Available (in Portable Document Format [PDF]) from the [American Academy of Sleep Medicine Web site](#).

Print copies: Available from the Standards of Practice Committee, American Academy of Sleep Medicine, One Westbrook Corporate Center, Suite 920, Westchester, IL 60154. Web site: www.aasmnet.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on April 25, 1999. The information was verified by the guideline developer on May 24, 1999. This summary was updated by ECRI on October 22, 2001. The update information was verified by the guideline developer as of November 21, 2001.

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Date Modified: 11/8/2004

The logo for FIRSTGOV, with "FIRST" in blue and "GOV" in red, and a small red star above the "I".

